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Narratives in Oncology

Oncology in 2050 – A Retrospective?

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Introduction

Progress in oncology over the last 30 years was like hiking up an inhospitable mountain. Advances were painfully incremental, but looking down from the summit now certainly gives a sense of achievement. Granted, there were no "eureka" moments that defined sentinel understandings in cellular biology or cancer pathophysiology, but rather steady improvements in technology, pharmacology, and supportive care.

Preventive Oncology

There have certainly been advances in treatment for almost all types of malignancy, but the development of "preventive oncology" and its incorporation into public health, education, and policy from the late 2030s has impacted multiple cancers. Preventive oncology as a specialty was championed and developed initially by the European Society for Medical Oncology (ESMO) from 2032 following an infusion of public health funding for cancer as part of the "BRentry" package. The rationale was that specialized expertise in epidemiology, oncology, and genomics was needed to provide appropriate advice to patients on lifestyle and pharmacological risk management. The dramatic increase in availability of over-the-counter genome testing, initially for specific high-risk defects but subsequently to identify even minor genetic features that influenced susceptibility to both malignant and nonmalignant disease, also drove its development. A pivotal moment was the 2038 report of the "Twin Cities" (Minneapolis–Saint Paul) study, the first of several randomized trials that demonstrated statistically significant and meaningful reduction in deaths from malignant disease in patients with even subtle increased germline risk randomized between active and passive management [1].

As part of genomic risk management, "liquid biopsy" has moved from being a therapeutic to a diagnostic tool and finally to a public health screening tool. Its impact on patient care emerged slowly: initial profiling back in 2018 was inconsistent among providers [2], but increases in accuracy provided reliable characterization of oncogenes and biomarkers that were able to identify potential sites of occult malignancy. Concurrent development of P-oxybenzoid targeted ultra-temporal summation (POTUS) positron emission tomography (PET) allowed high-resolution imaging of sites of potential malignancy identified by liquid biopsy, thereby diagnosing many malignancies while submillimeter and localized. Not surprisingly, POTUS-PET technology has also been applied as a screening tool in people at high risk for cancer. Initially funded during the fifth term of the Trump administration, the MAGA-MAGAS (Multiplex Assessment of Great Accurate iMaging And Glorious Answers to Stuff) trial tested this strategy with the results expected to be announced later this year.

Theranostics

Related to PET, the impact of theranostics has increased substantially. Following several small but encouraging trials from 2017 onwards [3, 4], theranostics has evolved with the development of appropriate ligands and particle therapy. The advent of OxyFullerene Flexible Adjunctive Ligand (OFFAL) technology has allowed varying ratios of encapsulated alpha and beta particles to be ligated to antibodies and peptides, individualized for each patient's tumor cells. The greatest utility of this OFFAL therapy has been in avoiding deforming surgery for sarcomas, which can be downsized to reduce the morbidity of a planned excision. We now talk of "nuclear surgery"—although there is competition between radiation oncologists and nuclear medicine physicians regarding the term; radiation oncologists restrict its use to nanoparticle chemistry that directs the release of high partial pressures of oxygen to an area that is being irradiated, thereby significantly augmenting the activity of external beam radiotherapy.

Immunotherapy

The goal of "making cold tumors hot" and thereby allowing a marked increase in response to immunotherapy was achieved finally in 2030 with the development of two new technologies. Quantification and amplification of an antitumor immune

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response was enhanced by the ability to define a priori antigenic determinants and cytotoxic potential of CD8+ cells through Stapled eXcitable ytterbium (SeXy) cytometry, allowing targeted vaccination. Inducing an effective immune response proved more difficult, as the immune system of patients with cancer is subject to many failures in the steps between antigen generation and the development of effective T-cell clones. The solution to this problem required development of ex vivo Immune Mimicking Holistic OrganizaTion (IMHOT) presentation systems. These IMHOT "incubators" exposed tumor samples to optimized antigen-presenting cells, which then interacted with off-the-shelf "naked" T cells, with appropriate cytokine support to develop an amplified immune response to the cancer. The iterative nature of the process allowed the development of a broad immune repertoire against most cancers. IMHOT treatments achieved cascading approvals from the U.S. Food and Drug Administration from 2029 onwards and eliminated the use of chimeric antigen receptor T-cell technology, even the eighth-generation versions that appeared in the early 2030s that eliminated the troublesome cytokine release syndrome and neurotoxicity.

Some surprises arose along the way in immunotherapy; the incorporation of Cysteine Hydroxy-Ether Adamantane Piperazine (CHEAP) technology that facilitated drug release only in the tumor microenvironment increased the therapeutic ratio of several repurposed medications—the unforeseen 2035 approval for CHEAP-metformin allowed its local tumor release to delay intratumoral T-cell exhaustion, thereby improving the outcome of most immunotherapies [5].

Chemotherapy and Targeted Therapy

Chemotherapy for cancer was used rarely by the mid-2040s and only as a treatment of last resort. The CHABNER study (Chemotherapy After our Best and Newest Rx) presented by the editor of this journal in 2046 (yes, people are living longer) demonstrated no survival or quality of life improvement when chemotherapy was added after contemporary treatment, thereby cementing its demise [6].

Molecular pathways that had been difficult to target became amenable to therapeutic inhibition, resulting in a rash of pantumor approvals. *RAS* mutations proved ultimately to be targetable, albeit well past 2035, most of the responsible small molecules coming from Chinese pharmaceutical companies. In a landmark announcement in 2042, the *New England Web of Medicine* reported three simultaneous practice-changing studies in which RAS inhibitors, used in combination with standard-of-care regimens, improved overall survival of *RAS*-mutated malignancies [7–9].

Other advances have been equally profound; Von Hippel–Lindau mimetics are now used universally (in combination) for treatment of metastatic renal cell carcinoma with substantial improvements in survival. Potent telomerase inhibitors that do not cause thrombocytopenia are now in use as adjuncts to several standard therapies, as well as NF-κB inhibitors, which curiously cause severe grade 3 nightmares, likely because of structural similarities to mefloquine (grade 3 nightmares, according to Common Terminology Criteria for Adverse Events version 10.0, are characterized by waking a partner from sleep or bedwetting as a result thereof). An unexpectedly useful class of drugs includes derivatives of the radioprotector amifostine. Firmitostine, statherostine, and roburostine are effective inhibitors of chromosomal instability that characterize the malignant progression of many malignancies. The key side-chain modifications that allowed oral administration and eliminated the mild hypotensive side effects led to their widespread adoption.

Unfortunately, there has been less success in targeted therapies for other cancers. Adult acute lymphocytic leukemia remains refractory; 5-year survival rates remain only about 70% after the initial advances with radiolabeled alpha conjugates such as 223-medelalumab that have been used since the late 2030s [10]. Despite novel tri-specific combinatorial immunotherapy such as moribundumab from 2025 and lysosomal disruptors such as reprehensazole from 2045 [11], high-grade serous ovarian cancers still recur, and nothing has replaced debulking surgery as the upfront treatment.

Pathogenesis of Cancer

Advances in understanding the pathogenesis of cancer have been impressive, in particular the report by Adams and Dent [12] that defined the 42 chemical carcinogens in the environment that accounted for all the previously unexplained mutational signatures of cancer now identified [13]. Reviews of cancer pathophysiology in the third and fourth versions of "The Hallmarks of Cancer" appearing in 2023 and 2038 indicate that the behavior of a tumor is governed by much more than its genome. Improved proteomic analysis derived from the mass spectrometry technology described in 2017 [14] was used as a discovery and validation tool for targeted therapy from 2025 onwards. So-called "quiet" genomes were found frequently to be chaotic at the protein level. This spurned global efforts to work with artificial intelligence (AI) platforms to associate proteomic profiles with clinical variables, including pharmacodynamic effects of drugs. The American Society of Clinical Oncology (ASCO) CancerLinQ version 2.0 that launched in 2025 accumulated sufficient data on the proteome to direct therapy of several tumors after 2035. Introduction of the AI component in version 3.0 in 2040 nicknamed "HAL" (Heuristic ASCO aLgorithm) could be disconcerting ("This treatment is too important for me to allow you to jeopardize it" or "This prescribed treatment can serve no purpose anymore. Goodbye") but proved useful clinically in synthesizing gigabytes of information into an informed treatment decision.

Approval and Pricing of New Therapies

Increases in patient longevity, multiple available treatments, and drug expenditure eventually spurred global efforts to control drug pricing. Project Orbis, the global drug approval mechanism that debuted in 2019 [15], evolved and subsequently recommended a global, value-based framework for pharmaceutical pricing, which was proposed during the G20 summit of 2022 in New Delhi. It was incorporated into the Australian and Canadian health systems in late 2028 and other G20 countries in 2030. Orbis version 2.0 allowed

collective bargaining on a global scale between governments, insurers, and the pharmaceutical industry and achieved significant success in controlling drug pricing. Drug approval also became more selective. In 2024, ASCO and ESMO coordinated their scales for assessing clinical value, and in 2028 regulatory agencies responded to critical opinion and accepted the unified ASSESS-V criteria for approval of new treatments [16]; this was in belated recognition that a simple statistical test giving $p < .05$ measures neither the size of an effect nor its importance. Absolute differences in overall survival of ≥5% compared with control values and/or unequivocal improvements in quality of life are now required to warrant approval of new drugs.

Environmental Issues

There has been increasing appreciation of the importance of the environment as a key determinant of human health. The relocation of the workforce to rural areas following the COVID-19 pandemic in 2020–2022 and the almost complete disappearance of the internal combustion engine, together with continued reduction in smoking (now banned in Australia, Canada, and New Zealand), has led to a dramatic reduction in incidence of lung and other smoking-related cancers. More surprising was a substantial reduction in incidence of pancreatic cancer for reasons that are poorly understood but thought to relate to unidentified pollutants. The "host" remains critical: vaccination against common human leukocyte antigen–restricted peptides in key cancer oncogenes has reduced cancer incidence in certain populations. Human papillomavirus vaccination eliminated almost all malignancies of the cervix and oropharynx in Western countries, although the zika-assOciated MaliGnancies (OMG), which appeared suddenly from 2030, offset these gains. This neurotropic virus, resulting from a random combinatorial event with the human T lymphotropic virus type 1 genome, leads to development of giant cell glioblastomas, particularly in the sub-Saharan population. Fortunately, its incidence has decreased recently, likely because of ecologically driven reduced virulence rather than the multiple efforts at eradication.

In 2050, the authors of this report, living some 15,000 km apart, will probably never again meet face to face. Frequent hurricanes and typhoons along the American and Chinese coasts from 2027 onwards and rising sea level forced mass migration from coastal areas. At the Thunberg convention, convened hastily at the Relocated University of Miami at Denver (RUMAD) in 2030, governments had little choice but to impose massive taxes on all forms of carbon emission, currently 300% for air travel. The role of face-to-face meetings was already in decline following the COVID-19 pandemic and was cemented following the variant H1N1 scare in 2025; by 2026 most oncologists paid for the live-streamed version rather than attend the ASCO or ESMO annual meetings. These and other societies have held only virtual meetings since 2030, and all journals ceased to publish paper editions by this time. However, ASCO and other professional organizations continued to rise in importance as purveyors of practice-changing trials. The establishment of the Targeted Agent and Profiling Utilization Registry (TAPUR) in 2018 [17] demonstrated the ability of ASCO to execute clinical trials, and by 2026, contracts with both insurers and governments established trials with cost-saving endpoints. These trials demonstrated equivalent therapeutic effects using less frequent scheduling and markedly lower doses of drug such as immune checkpoint inhibitors, ibrutinib, and abiraterone, thereby allowing greater access to these effective drugs, even in poorer countries.

Beyond 2050

What do the next 25 years hold? It is difficult to make predictions—"I only predict the things I don't know will come true" was Boris Johnson's 2030 quip about his chances of entering his third term as Great Britain's prime minister (Scotland seceded in late 2028), but there are some indications about the future path of oncology. "Genome reconstitution" with Tandem Aligned Sequence Targeted Integrated Reagent (TASTIeR)—the successor of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)—is becoming a reality. The uptake and forced integration of wild-type oncogenes such as *p53* and *RB* into the tumor genome has had almost curative effects in early trials, regardless of tumor type. In 2050, the outcomes of cancers have become mostly predictable. In-depth genomics and proteomics, serial biomarker monitoring, and the wealth of open-source information about previous patients with similar cancers has facilitated the use of early, accurate, and highly effective therapies, thereby turning cancer into a chronic disease. The next decade is even more promising. The mountain is indeed smaller.

Disclosures

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References

1. Thaneswaran S, Ballinger M, Kummerfeld S et al. Active compared to passive intervention following whole genome sequencing analysis: A phase 3 trial. e-JAMA Oncol 2038;345: 56–65.

2. Torga G, Pienta KJ. Patient-paired sample congruence between 2 commercial liquid biopsy tests. JAMA Oncol 2018;4:868–870.

3. Strosberg J, El-Haddad G, Wolin E et al.; NETTER-1 Trial Investigators. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. N Engl J Med 2017;376:125–135.

4. Hofman MS, Violet J, Hicks RJ et al. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): A single-centre, single-arm, phase 2 study. Lancet Oncol 2018;19:825–833.

5. Petrella T, Monzon J, Shackleton M et al. CHEAP-metformin in first-line immunotherapy for metastatic melanoma: Results of a combined phase 3 trial of MASC and NCIC-CTG. e-JAMA 2035;873:44–52.

6. Chabner B, Sartor OA, Bates SE et al. CHABNER study (CHemotherapy After our Best and NEwest Rx): Results of a phase 3 trial with survival and qualitative outcomes. e-JAMA 2046; 11:e314–e325.

7. Chin V, Knox J, Julandin S et al. Shenqiazole and improvement in overall survival in K-RAS pancreatic carcinoma. N Engl Web J Med 2042; 36:35–43.

8. Barnet M, Natpilli L, Thi M et al. Qishiatib in KRAS mutant colorectal cancer: Results of a phase 3 study. N Engl Web J Med 2042;36:24–34.

9. Sim H, Yang G, Gadgaard MG et al. Wanxioastine in RAS mutant NSCLC compared to

physicians choice: A randomised phase 3 study. N Engl Web J Med 2042;36:44–49.

10. Lavee O, Moore J, Hamad N et al. 223-Medelalumab and overall survival in refractory acute lymphocytic leukemia: An Australian Leukemia and Lymphoma Study Group Protocol 648. e-Lancet 2038;564:45–53.

11. Beale P, Mackay H, Lheureux S et al. Reprehensazole in platinum-refractory ovarian cancer: An intergroup study of the NSGO, EORTC GCG and NCIC-CTG. e-Lancet Oncol 2045;78: 456–459.

12. Adams D, Dent A. Final delineation of causes of mutational signatures in cancer - with environmental correlates. N Engl Web J Med 2035;451:23–34.

13. Alexandrov LB, Kim J, Haradhvala NJ et al.; PCAWG Consortium. The repertoire of mutational signatures in human cancer. Nature 2020; 578:94–101.

14. Anjo SI, Santa C, Manadas B. SWATH-MS as a tool for biomarker discovery: From basic research to clinical applications. Proteomics 2017;17:1600278.

15. Project Orbis. U.S. Food and Drug Administration Web site. https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis.

16. Prasad V. Reflections on 20 years of banging at a closed door - Progress in drug approval in the United States. e-JCO Precis Oncol 2028;87: 34–35.

17. Mangat PK, Halabi S, Bruinooge SS et al. Rationale and design of the Targeted Agent and Profiling Utilization Registry (TAPUR) study. JCO Precis Oncol 2018. https://doi.org/10.1200/PO.18.00122.